**Airway Pharmacology**

**I Asthma and COPD**

**Asthma: LM: SMC prolif and mucus secretion, Creola bodies (epithelial shedding), Curshmann spirals (mucus with epithelial cell/debri), CL crystals**

This is a chronic inflammatory disease of the lung due to hyper-reactivity to certain substances. PT suffer from acute attacks which can be fatal (nocturnal attacks are not uncommon). There are various triggers: allergens, viruses, exercise, drugs (aspirin, **tartrazine dye**, BB), GERD. The character of the disease is classified as intermittent or persistent based on the frequency of the attacks (less than2xa week, more than 2x a week). Severity is determined by the impact on lung function between attacks (>80%, 60-80%,<60%).

Pathophysiology: activated mast cells release mediators which induce bronchoconstriction, vasodilation, increased permeability, inflammation. Histamine**, LTD4**, PGD2, Platelet activation factor, Acetylcholine all increase contraction in the bronchial smooth muscle by way of **Gq.** The vasodilation effects and edema are mediated by the LTD4/C4, histamine, PGD2 while **LTB4** is a chemoattractant for inflammatory cells and activates Neutrophils and eosinophils. Drugs need to target the lungs ONLY. Best drugs are inhaled and have a local effect (prob, 80% of inhaled is swallowed so must not be absorbed by the gut or need a high first pas metabolism).

PHASES: acute phase is characterized by immediate bronchoconstriction dueto mast cell activation. Late phase is due to the influx of inflammatory cells. The late phase occurs 50% of PT, 6-10hrs after the attack with pro inflammatory cytokines being released as a result of TNFalpha. **LTD4** is responsible for increases in mucus production and impairment of cilia (ECP, MBP also stop cilia).

Chronic response leads to hyperactivity to histamine and acetyl choline (**methyacholine** can mimic acetylcholine and used as a diagnostic). Airway remodeling is not completely reversible and includes:

* Epithelial prolif
* Increased goblet and mucous glands
* Collagen deposition leading to thickened BM
* SMC hypertrophy

**BRONCHODILATORS:**

**Beta Adrenergic Agonists**: relax the SMC of airways by B2 activation of Gs to increase CAMP and decrease intracellular Ca. There are important side effects like sinus tachycardia (10-50% of receptors on the heart are B2), tremor, N/V, Hypokalemia (muscles take up K), hyperglycemia. Tachyphylaxis is also an issue due to down regulation of B2receptors.

1. Epinephrine: first drugs to treat asthma and full alpha/beta selectivity which can produce significant sideRX. Cannt be taken orally due to COMT metabolism. Currently only used for emergencies.
2. Isoproterenol: Beta selective and resistant to COMT. It causes excessive cardiac stimulation so no longer a good therapy.
3. Albuterol and Terbutaline: **Rapid onset, 2-3 hour use, most important subtype.** Both of these are derivatives of epinephrine with increased t1/2 and B2 selectivity. Albuterol is not given oral or inhalation while Terbutaline is oral/parenteral/inhalation.
4. Levalbuterol: it is albuterol but only in the R-enatiomer. Supposedly less side RX and PT needs a lower dose… but to expensive for small advntg.
5. Salmeterol (LABA) and derivative Formoterol: B2 selective, slower onset, not used in acute exacerbations but prophylaxis **2x daily** (duration12hrs). **Black box warning: not used in acute, and needs to be used with gutacortacoids only to restore PT to stable base line. Can be used as a monotherapy still for COPD. Monotherapy in asthma increases risk of resp-related death.**
6. Arformoterol and Indacaterol: these are B2 selective (Renatntiomers) that are **only used for long term therapy of COPD**. Longer half-life reduces Indacaterol to **1x daily**.

**Anti-Cholinergics**: parasympathetic pathways cause bronchospasm in COPD and Ach causes mucus secretion in Asthma. Decreasing muscarinic activity (just like increasing sympathetic activity) should allow the lungs to expand more easily. It is assumed that somehow vagal stimulation by irritants increase the parasympathetic tone on M3 receptors to increase Ca levels. Side effects include dry mouth and other decreases in parasymp activity.

1. Ipratroprium: analog of atropine that is inhaled (much like jimson weed) and doesn’t entero the GI or CNS. Its onset is very slow and can be used for bronchospasm of COPD and sometimes asthma if secretions are excessive. Often it is combined with albuterol and given **4x daily**. It can be used as a rescue therapy if PT no responsive to SABA. (some nasal sprays use this to help with rhinorrhea).
2. Tiotropium: analog of scopolamine has a 24 hr t1/2 so given **1x daily**

**Glucocorticoids:** part of the body’s natural anti-inflammatory. They do not directly induce bronchodilation. Three primary functions: inhibit inflammatory cell prolif (block transcription in the nucleus by binding GR and removing it from HSP90), decrease leukocyte recruitment by inhibiting pro-inflammatory cytokine production, and prevent B2 down regulation while promoting upregulation (helps combat Tachyphylaxis in BA). 10% of PT can be insensitive (FEV1 does not improve 15% in 7 days). Typically given as **Short term (oral/IV 3-10days)** or **Long term (Inhalation or rarely systemic).** First line therapy for mild/moderate persistent asthma as a monotherapy or combined with LABA in moderate/severe persistent asthma. Side effects are Iatrogenic Cushing’s, HPA Axis Suppression, Oral candidiasis

* **Iatrogenic Cushing’s syndrome**: same SX as Cusings since both are caused by excessive amounts of gluticorticoid. **SX:** moon facies, buffalo hump, fat in the trunk, muscle wasting, **osteoporosis**, hirsutism, cataracts/glaucoma, thin skin and CNS issues with diabetes.
* **Hypothalamic-Pituitary-Adrenal Axis Suppression (HPA):** decreased endogenous GC production (feedback inhibition), atrophy of cells in the cortex… abrupt withdrawl (after long term use) leads to adrenal insufficiency. Withdrawl of drug slowly and give supplements during stress.
* **Oral candida** is VERY common with inhaled drugs due to decrease immunity in the oral cavity. PT presents with hoarseness, cough (tell PT to rinse mouth after inhalation.

1. Prednisone and methylprednisolone: therapeutic response in 6hrs makes it great for treating the late phase if given at the onset of acute phase. Pred is converted to prednisolone in the liver (keto->alchol). Methylpred can have different additions to allow for oral, IM or IV.
2. Triamcinolone Acetonide: as the name implies… this is an acetonide derivative used locally or can be given IM. They have better absorption
3. Fluticasone and Budesonide: inhalation with a variable onset of action from days to weeks. Only used for prophylaxis. Oral bioavailability is 9% with 18-20% with inhalation. (Flonase, Rhinocort used as an allergy nasal spray)

**ANTI-INFLAMMATORY AGENTS**

**Anti-leukotrienes**: LTD4 is the most potent bronchoconstrictor, stimulates mucus secretion, inhibits cilia and causes increased vascular permeability. These drugs have a slow onset, bind to the LT receptor (1 and 2) and are given orally. They are the alternative/additive to GC therapy (but are not preferred over GC). May have some liver issues, increased Churg-Strauss, mood changes. Some block the 5’lipoxygenase like Zileuton

1. Zafirlukast: oral tablets **2x daily** with drug interactions due to CYP2C9 and 3A4 inhibition. SOME cases of liver toxicity.
2. Montelukast: same as above but some advantages are **1x daily**, chewable cherry tablet for 2yr olds, doesn’t inhibit the CYPs and no evidence so far no liver toxicity.
3. Zileuton: inhibits ALL leukotrienes and only used prophylactically to prevent acute attacks and decrease the need for SABA. Oral activity but high first pass metabolism. It does inhibit **Theophylline (bronchial relaxation), Warfarin, Propranolol** blocking the CYP1A2 to decrease clearance increasing t1/2

**Mast cell stabilizers**: inhibit mast cell degranulation, autacoid production and synthesis of proinflammatory cytokines. It takes several weeks to reach their full effect. They are less effective than GC and more of a back-up drug. Treat asthma, rhinitis, ulcerative colits, conjunctivitis (all with low efficacy).

1. Cromolyn Na, Nedocromil, pemirolast

**Methylxanthines**: naturally occurring compounds that cause bronchodilation and are anti-inflammatory. They are NOT used for rescue therapy, are given IV or oral and work by increasing levels of CAMP. There is a narrow therapeutic window that requires individualized therapy per PT. The effects are some CNS side effects or GI effects as well as Arrhythmias and seizure.

1. Theophylline: still GC preferable; alternative to B2 agonsits. It can be combined with B2 agonists and systemic glucocorticoids for acute exacerbations of Asthma. It is a **SLOW RELEASE** reducing the dosing frequency. The narrow therapeutic window means that high doses can be fatal with Cardio effects, GI, Metabolic and CNS. In overdose: multidose charcoal, whole bowel irrigation, propranolol (for B effects), Diazepam (decrease seizures) and hemodialysis if plasma over 100mg/L
2. Roflumast: same as theophylline but more selective and sued for sever COPD associated with chronic bronchitis. This particular drug inhibits PDE4. Be aware it could cause GI effects, weight loss, headache, insomnia and suicidal ideation.

**Anti-IgE: Omalizumab** is a chimeric antibody to the Fc of IgE. Given SC to PT with mod-severe allergic asthma that isn’t well controlled with steroids.

**II. Drugs for Pulmonary Hypertension**

**Pulmonary arterial hypertension:**

Primary pulmonary hypertension or secondary (scleroderma/autoimmune) resulting in poor quality of life due to inadequate delivery of O2. Leads to Cor Pulmonale. Treat with Anticoag, Vasodilators (CCV, ACEI), Diuretics, Digoxin as well as these:

**Prostaglandin**

1. Epoprostenol: very short t1/2 requires continuous IV; can have flushing, hypotension, N/V/D, rebound hypertension (after abrupt withrawl)
2. Treprostinil: longer t1/2 and given by SC infusion or inhalation
3. Iloprost: also longer than Epo but less than Treprostinil

**Endothelin antagonists**

1. Bostentan: oral, blocks ETA&B to produce vasodilation and bronchodilation; **Hepatotoxic, Birth defects, CYP3A4 increased activity, decreased Statin activity, CYP3A4 blockers increase its hepatotoxicity.**
2. Ambrisentan: same

**PDE 5 Inhibition**

1. Sildenafil and Tadalafil: both are oral and give once daily.

**III. Cough suppressants, Expectorants and Drugs for Allergic Rhinitis**

**Antitussive:** These compounds are used to suppress cough and not to be used in asthma, emphysema or smokers. Require CYP2D6 to be active

1. Codeine: acts in the CNS to elevate the threshold to induce cough. CYP2D6 metabolizes the drug to its active form. Cough suppression occurs at doses less than analgesic doses.
2. Dextromethorphan: unlike Codeine, its effect cannt be antagonized by Naloxone. These have little effect on gut motility and blocks re-uptake of serotonin with duration upto 5-6 hrs. But it is metabolized to its active from by CYP2D6. **Drugs like fluoxetine and paroxetine block CYP2D6. These shouldn’t be used with MAOI and can produce CNS effects.**

**Expectorants:**

1. Guaifenesin: the only expectorant that actually has demonstrated its efficacy; it decreases the viscocity and increases cilia activity

**Allergic Rhinitis:** inflammation of the nasal mucosa, sneezing, runny nose, itching and congestion (dilation/engorgement of BV). Classified as seasonal or perennial and drugs that treat asthma are similarly beneficial for treating allergies.

1. Glucocorticoids: nasal sprays (Beclomethasone, Fluticasone, Triamcinolone)
2. Cromolyn sodium: less than GC but can be used prophylactically with 1-2 weeks to take effect
3. Sympathomimetics: alpha 1 receptor agonist (Phenylephrine, pseudoephedrine, phenylpropanolamine)
4. Anticholinergics: Iprtroprium bromide
5. Antileukotrienes: montelukast
6. Antihistamines: see histamine notes